

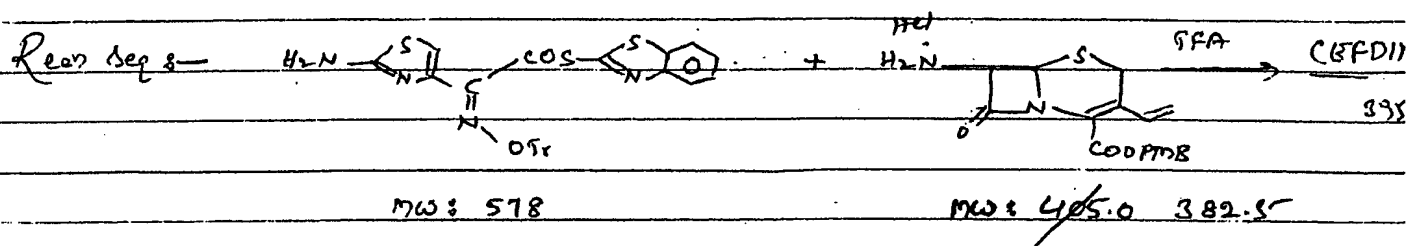
## EXHIBIT A

94

## Condensation and Deprotection

PR(094) 94

Objective: Preparation of Condensed Amide.



S.No	Raw materials	mole wt	mole	Amount	mol. ratio	Source
1	7-AE-HI salt	405	0.0452	20 gm	1.0	
2	DMAC	382.5	—	100 ml	51	comm
3	Thio ester	578	0.0493	28.5 gm	1.0	PR/88
4	TFA	114	—	105 ml	31	comm.

Procedure:— DMAC was added at RT.

Thio ester was added in one lot at the same temp.

The mix was stirred for 5 min.

Almost clear solution was formed.

HI salt was added in one lot.

Stirred the mix for 2.0 Hrs at 40-50°C. (pH was maintain ~ 3-4) F 28A

The was showing ~ 2-3 % of H<sub>2</sub>O.

Reo mix (clear soln) was cooled to 10°C.

DCM was added (250 ml) at the same temp.

DM H<sub>2</sub>O (250 ml) was added in one lot at 10-15°C.

Stirred for 5 min.

Layers separated.

Aqueous layer was again extracted with 250 ml of DCM.

Combined organic layer washed with DMAC (100 ml x 3) + 30 ml brine.

Organic layer washed with 1% NaOH soln for 1.0 Hr.

layers separated.

Organic layer washed with brine sol<sup>n</sup> (100 ml).

DM was distilled off at below atm. v. vac.

To get the 'dark coloured' residue.

To HPLC toluene (400 ml) was added and condensed ~100 ml v. vac.

Solvent layer was cooled to 10°C.

TFA was added over a period of 30 min at 10-15°C.

After add<sup>n</sup>, stirred the mix at 15°C for 3.0 hrs.

Dark coloured react<sup>n</sup> mix was cooled to 0°C.

DM H<sub>2</sub>O (350 ml) was added and stirred for 15 min.

Layers separated.

Note: - During the layer separation, solid was formed.

the pH was adjusted to 4.5 by adding AgNH<sub>3</sub> sol<sup>n</sup>.

Then layers separated.

Aqueous layer was cooled to 10°C.

Carbon (2 gms) was added and stirred for 30 min.

Filtered through <sup>hydro</sup>carbon, washed with DM H<sub>2</sub>O (50 ml).

Filtrate (A<sub>1</sub>) was cooled to 10-12°C.

pH was adjusted to 1.1 by using conc HCl sol<sup>n</sup>.

White solid was obtained.

Stirred the mix for 30 min at 0-5°C.

Solid was filtered, washed with Me (50 ml).

Solid was treated with 350 ml of DM H<sub>2</sub>O at 30-32°C for 30 min.

Then cooled to 0-5°C for 30 min.

Filtered the solid, washed with DM H<sub>2</sub>O (50 ml) (5°C).

Dried the solid at 35-40°C v. high vacuum for 5 hrs.

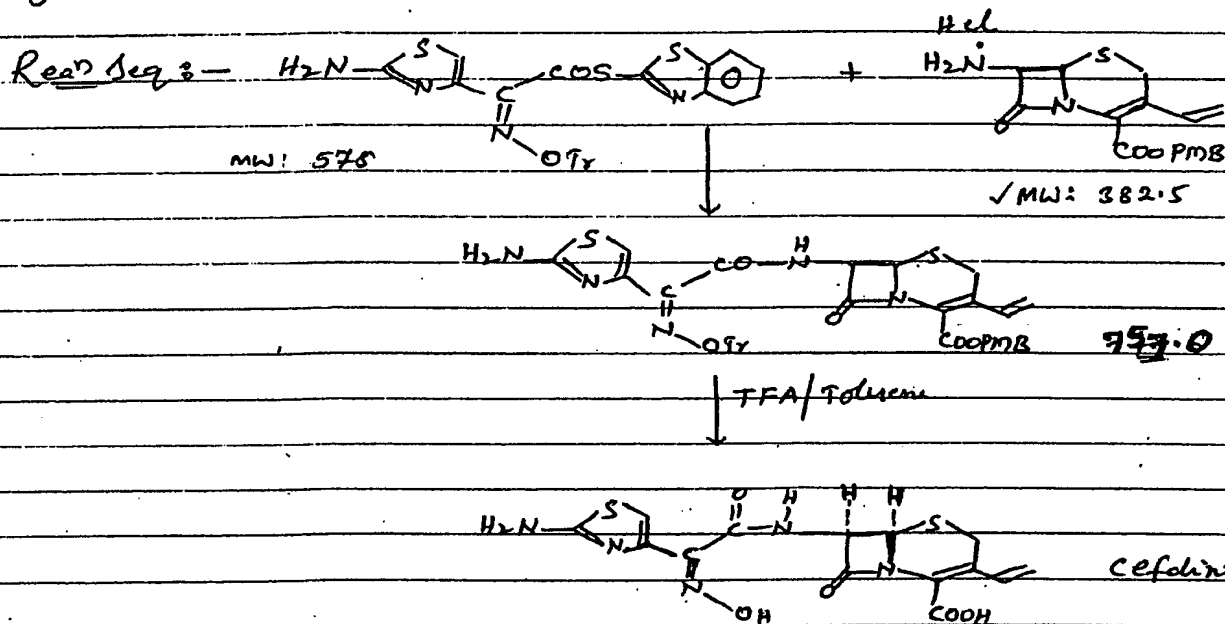
Dry wt = 9.0 gm

HPLC Assay (OAB): 98.45% (m/c: 7.59%) ~~98.45%~~

## Cefdinir

PR(094) 98

Objective:- Preparation of Cefdinir. (Repetition of PR(094) 94)



S.NO	Raw materials	mole wt	moles	Amount	mol. ratio	Source
1	A.E. Hel salt	382.5	0.130	50 gm	1.0	
2	Thio ester	578	0.124	71.5 gm	0.95	
3	DMAc	—	—	250 ml	5T	
4	CH <sub>2</sub> Cl <sub>2</sub>	—	—	1.25 lit	25T	
5	NaOH (1% aq)	40	—	500 ml	—	
6	Toluene	—	—	1.0 lit	—	
7	Carbon	—	—	10 gm	—	
8	TFA	114	—	300 ml.	—	
9	Toluene	—	—	400 ml.	—	
10	DM H <sub>2</sub> O	—	—	1.2 lit	—	
11	Aq. NH <sub>3</sub>	—	—	—	—	
12	—	—	—	—	—	

Procedures— DMAc was added at RT.

A-E. Hcl salt was added in one lot at the same temp.

The mix was stirred for 5 min, clear solution was formed (PH = 1.6).

To this Hcloster was added in one lot at the same temp.

The mix was stirred for 10 min at 25-26°C.

PH comes down to 1.4.

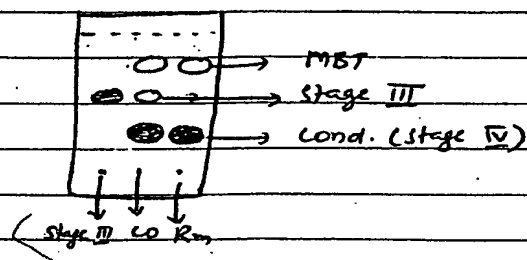
Temp was raised to 45-50°C.

Maintained for 2.0 Hrs exactly, during the maintaining PH was maintained ~ 1.75 to 2.1 by adding TEA.

Rec was monitored by TLC and was showing the absence of stage III

TLC System— EtOAc : Hexane

2.5 ml : 2.5 ml.



Then the "Rn" was cooled to RT.

"Rn" was poured into the mix of 1.0 lit H<sub>2</sub>O + 750 ml of DCM.

The mix was stirred for 10 min at 20-25°C.

Layers separated.

Aqueous layer was extracted with 500 ml of DCM.

DCM layer (combined) washed with DM H<sub>2</sub>O (500 ml x 3).

Then to the organic layer, NaOH soln (1%, 500 ml) was added over a period of 30 min.

Stirred for 1 1/2 Hr at 25-26°C.

The mix was Passed through the hyflow bed.

layers separated (not clear), DCM (500 ml) was added.

Organic layer washed with 200 ml DM H<sub>2</sub>O

Then concentrated to get the residue at 34-36°C u/ vacuum.

To the residue, toluene was added (1.0 lit)

Again distilled the toluene (200 ml), to remove the traces of DCM

Toluene layer washed with H<sub>2</sub>O (200 ml x 2).

Carbon (5 gm) was added to the organic (toluene) layer.

stirred for 15 min at 30-35°C.

filtered through the hyflow bed, washed with 50 ml of toluene.

Toluene was distilled off u/ vacuum till 600 ml of toluene was remains inside the flask (To remove the water).

⇒ Organic layer was kept for overnight at RT.

Organic layer was cooled to 10°C.

TFA (300 ml) was added over a period of 10-15 min at 10-15°C.

After the add<sup>n</sup> is completed, the temp was raised to 18-19°C.

Maintained for 3.15 Hrs., Toluene (400 ml) was added.

Then the react mix was cooled to 0-5°C.

DM H<sub>2</sub>O (1000 ml) was added at below 20°C. Over a period of 5

\* Temp should be 18-20°C (at the end of the H<sub>2</sub>O add<sup>n</sup>).

After the add<sup>n</sup> immediately layer separated.

Aqueous layer was kept in ice + H<sub>2</sub>O mix (5-10°C).

Organic layer washed with 300 ml of DM H<sub>2</sub>O.

layer separated.

combined <sup>aqueous</sup> organic layer was cooled to 0-5°C.

pH was adjusted to aq  $\text{NH}_3$  soln ( $\sim 425 \text{ ml}$ ) at below  $20^\circ\text{C}$  ( $15-20^\circ\text{C}$ ).

At the end of the aq. pH should be  $5-5.5$ .

At this pH almost clear solution formed. containing brownish undissolved particles.

Now add activated carbon ( $5.0 \text{ gm}$ ) at  $15-20^\circ\text{C}$ .

Temp brings down to  $10^\circ\text{C}$ .

Maintained for 30 min.

Filter the carbon, through hyflow bed ( $15 \text{ gm}$ ).

Washed the bed with  $50 \text{ ml}$  of  $\text{DM H}_2\text{O}$ .

filtrate (aqueous layer) was cooled to  $10-15^\circ\text{C}$ .

Adjust the pH 1.0 by adding conc HCl solution.

Maintain the pH 1-1.1 for 1.0 Hr at  $0-5^\circ\text{C}$ .

Filter the solid, wash, suck dry. - still lot drop.

Take the wet cake ( $85 \text{ gm}$ ) and  $\text{DM H}_2\text{O}$  ( $950 \text{ ml}$ ).

Warm the mix to  $30-32^\circ\text{C}$  for 30 min.

pH was adjusted to 2.97 by adding saturated  $\text{NaHCO}_3$  solution at  $30^\circ\text{C}$ .

Then was cooled to  $5^\circ\text{C}$ .

Stirred at this temp for 30 min.

Filtered the solid, washed the cake with  $100 \text{ ml}$  of chilled  $\text{H}_2\text{O}$  ( $5^\circ\text{C}$ ).

Dried the solid at  $30-40^\circ\text{C}$  w/ high vacu. for 10 hr.

Wet wt =  $56 \text{ gm}$

Wt of the dry product =  $24 \text{ gm}$

% m/c =  $7.1$

% Yield from HCl salt =  $49\%$

% Yield from GCE =

w/w Yield from HCl salt =  $0.48$

w/w Yield from GCE =  $0.36$